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14. ABSTRACT

The major goals and aims of this study are to investigate whether differences in cognitive outcome are related to mechanism of injury as well as white matter integrity using diffusion tensor imaging (DTI). We are also collecting and analyzing data in order to determine whether MR variables of interest are associated with psychosocial/clinical outcome, and whether there are group differences by mechanism of injury. Specifically, in the context of this study, we use novel, sophisticated MRI methods (e.g., quantitative diffusion tensor [DT] tractography) in order to characterize white matter changes seen within and across TBI subtypes, identify those at highest risk for poor outcomes, and gain knowledge about potential interventions to aid in recovery of brain functioning and cognition. In addition, we seek to identify the unique psychosocial challenges posed by differing mechanisms of injury as well as investigate the contribution of genetic factors (Apolipoprotein-E ε-4 [APOE ε4] and brain-derived neurotrophic factor [BDNF]) to brain integrity, neuropsychological functioning, and neurobehavioral outcome.

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INTRODUCTION

Aims and goals of the current project are to examine whether differences in neuropsychological outcome are related to mechanism of brain injury (blast versus blunt force) as well as white matter integrity using diffusion tensor imaging (DTI). We are also collecting and analyzing data in order to determine whether imaging variables of interest are associated with psychosocial/clinical outcome, and whether there are group differences by mechanism of injury. Specifically, in the context of this study, we use novel, sophisticated MRI methods (e.g., quantitative diffusion tensor [DT] tractography) in order to characterize white matter changes seen within and across TBI subtypes, identify those at highest risk for poor outcomes, and gain knowledge about potential interventions to aid in recovery of brain functioning and cognition. In addition, we seek to identify the unique psychosocial challenges posed by differing mechanisms of injury as well as investigate the contribution of genetic factors (Apolipoprotein-E ε-4 [APOE ε4] and brain-derived neurotrophic factor [BDNF]) to brain integrity, neuropsychological functioning, and neurobehavioral outcome.

BODY

Year 3: We have made considerable strides toward our stated goals as outlined in our Statement of Work. Our laboratory continues to grow at an exponential rate as we have expanded our collaborations and added key personnel. This year, we presented 8 studies at the International Neuropsychological Society meeting (Waikoloa, HI), and 1 study at the National Association for Neuropsychology (San Diego, CA). We expect to present another 5 TBI-focused studies at the International Neuropsychological Society meeting this February, 2014 (Seattle, WA). We now have 3 studies stemming from these data published or in press, and we expect to submit another 5 for review this Fall/Winter, 2013.

During this third year of our DoD study, we have recruited and tested roughly 36 participants who represent either combat controls or patients who have sustained mild to moderate TBI. There are an additional 9 participants that were screened, but not included given that they did not meet inclusion criteria (e.g., were excluded from participating). We have conducted approximately 260 phone screens, of potential subjects throughout the course of the study. To date, we have enrolled a total of 57 subjects. Our recruitment rate is typically about 2-3 subjects per month. Our attrition rate is close to 0; our study subjects are informed in advance about the duration of the study, so they almost always complete both the cognitive assessment and neuroimaging sessions. After scanning, data is immediately pre-processed and prepared for analysis by skilled staff with expertise in imaging processing and analysis techniques. Fidelity checks of the data collected are thus evaluated as it is collected given that processing occurs within a day or two of data collection. Ongoing recruitment of patients and collection of relevant neuropsychological and behavioral outcome data occurs in tandem with neuroimaging (collected within one week of scanning, after obtaining appropriate consents). Upkeep of regulatory approvals has also been necessary during this timeframe. Per our SOW, preliminary data analyses have been well underway over this past year.

Below is a summary of findings from the past year.

We found that a subgroup of mTBI participants with executive dysfunction demonstrated reduced white matter integrity of prefrontal white matter, corpus callosum, and cingulum bundle structures compared to mTBI participants without executive dysfunction. And, that participants

with TBI with loss of consciousness were more likely to show executive function difficulties and disrupted ventral prefrontal white matter integrity when compared to either TBI participants without LOC or control participants.

In examining factors that contribute to quality of life, we found that although cognition is important, negative mood is a particularly strong factor on predicting quality of life in veterans with mTBI. Affective symptoms, most predominantly fatigue appears to be the most relevant neurobehavioral symptom for predicting subacute quality of life.

The MFIS was found to be a valid multidimensional measure in evaluating both cognitive and physical fatigue in veterans with mTBI. Further, presence of post-traumatic amnesia may affect subtype of fatigue experienced by veterans with mTBI.

The fornix, a limbic structure that is particularly vulnerable to TBI-related diffuse axonal injury, was found to predict performance across several neuropsychological domains. Fornix volume was positively correlated with performance on attention, executive function, memory, and fine motor dexterity.

Findings from the Iowa Gambling Test study demonstrate that mild-to-moderate TBI is associated with subtle reward-related decision-making impairment, and they suggest that the IGT is a sensitive index of this aspect of executive dysfunction in veterans with mTBI.

Please find our two most recent publications in the appendix, and see the description below for a summary of each.

Schiehser et al 2013:

Postconcussive fatigue is reported in 50% - 77% of individuals with TBI and approximately 50% of those with TBI rate fatigue as one of their worst or most distressing symptoms. The Modified Fatigue Impact Scale (MFIS) is a self-report measure of fatigue symptoms and severity. This study advanced our understanding of TBI by being the first to statistically evaluate the factor structure and validity of the MFIS in a TBI population. We demonstrated via this study that the MFIS is a multidimensional measure that can be used to evaluate the impact of fatigue on cognitive and physical functioning following mild to moderate TBI. Findings revealed that the MFIS, as applied to TBI, best reflected two subscales that measure cognitive and physical fatigue and that it demonstrates high internal consistency and strong convergent validity with fatigue items on another commonly used measure. Thus, this study has the potential to advance research and improve clinical care for those who may with use the MFIS to evaluate, monitory and treat individuals with TBI and fatigue.

Sorg et al. 2013:

Improving our understanding of the mechanisms and factors associated with poor neuropsychological outcome is of great importance in the area of mild traumatic brain injury (mTBI) research and in clinical care. This study investigated the association between brain white matter integrity (via diffusion tensor imaging) and cognitive outcome in postacute mild traumatic brain injury (mTBI), specifically with respect to executive functions (EF) which may be particularly sensitive to mTBI. We identified a subgroup of OEF/OIF veterans with mild, but demonstrable, EF reductions (n = 13) and compared their measures of white matter integrity against mTBI participants without EF decrements (n = 17) and to control participants (n = 15). The subgroup of mTBI participants with EF decrements demonstrated significantly lower measures of white matter integrity in prefrontal, commissural and posterior association tracts. We also identified a history of loss of consciousness (LOC) versus alterations in consciousness (AOC) as a risk factor for EF decrements and disrupted prefrontal white matter integrity in mTBI. Importantly, these findings were not explained by psychiatric factors (i.e., PTSD or

depression). This study adds to the growing body of literature on mTBI outcomes and suggests that neuronal and cognitive recovery may be protracted in some cases of mTBI, especially in patients who experienced an LOC, and that poor cognitive recovery may be related to damage to brain white matter pathways.

All tasks listed above have been completed by the following personnel (Dr. Delano-Wood, Russell Kim, Elisa Lanni, and Norman Luc). Elisa Lanni and Russell Kim have actively recruited and enrolled participants. They also assist Dr. Delano-Wood in imaging data collection, processing, and analysis. Neuropsychological testing takes place within the Neuropsychology Unit at the VA San Diego as part of clinical care for each patient. Appropriate releases are obtained for access to those data. For any individual who was not tested clinically, we conduct a 2 hour neuropsychological battery of cognitive tests. Assessment has been coordinated by Dr. Delano-Wood, Elisa Lanni, and Russell Kim. IRB continuing review has been spearheaded by Dr. Delano-Wood and Russell Kim. Finally, Elisa Lanni has coordinated the genetic testing (buccal swabbing) for the project.

KEY RESEARCH ACCOMPLISHMENTS

- Altered white matter integrity contributes to reduced executive functioning in veterans with mTBI, and LOC may be a risk factor for reduced executive function as well as associated changes to ventral prefrontal white matter
- Negative mood is a particularly strong predictor of quality of life in veterans with mTBI – this supports the need for the systematic screening and treatment of cognitive and neuropsychiatric symptoms in this vulnerable population
- Modified Fatigue Impact Scale study show a strong convergent validity of MFIS scales with two Beck Depression Inventory (BDI-II) fatigue items. MFIS found to be a valid multidimensional measure that can be used to evaluate cognitive and physical fatigue in veterans with mTBI
- Specific neurobehavioral symptoms found to be associated with different self-reported ratings of QoL in veterans with mTBI. Affective symptoms appear to be the most relevant neurobehavioral symptoms predicting postacute QoL. Results have the potential to optimize targeted treatments to improve QoL in this vulnerable population
- mTBI group differs significantly from NCs on fornix FA as well as fornix MD, but not on fornix volume. Fornix DT indices positively correlates with performance on attention/working memory, executive functioning, and fine motor dexterity, and mTBI subgroup analysis of blast, blunt, and NCs subgroups significantly differed on fornix MD
- mTBI is associated with subtle reward-related decision-making impairment, and they suggest that the IGT is a sensitive index of this aspect of executive dysfunction in veterans with chronic TBI

REPORTABLE OUTCOMES

We have the following manuscripts and abstracts. The following studies were completed with joint funding from the VA and DoD.

Manuscripts Published or In Press:

Sorg, S.F., **Delano-Wood, L.,** Schiehser, D.M., Luc, N., Hanson, K.L., Nation, D.A., Lanni, E., Jak, A.J., Lu, K., Meloy, M.J., Frank, L.R., & Bondi, M.W. (Under revised review). White matter integrity in veterans with mild traumatic brain injury: Associations with executive function and loss of consciousness. *Journal of Head Trauma and Rehabilitation.* **(Delano-Wood: Corresponding Author).**

Schiehser, D.M., **Delano-Wood, L.,** Jak, A.J., Matthews, S., Simmons, S., Jacobson, M.J., Filoteo, J.V., Bondi, M.W., Orff, H., & Liu, L. (In press). Validation of the Modified Fatigue Impact Scale in Chronic Mild to Moderate Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation.*

Schiehser, D.M., Delis, D.C., Filoteo, J.V., **Delano-Wood, L.,** Han, S.D., Jak, A.J., Drake, A.I., & Bondi, M.W. (2011). Are self-reported symptoms of executive dysfunction associated with objective executive function performance following mild to moderate traumatic brain injury? *J Clin Exp Neuropsychol, 33(6), 704-14.*

Manuscripts Under Review:

Long-Term Neurobehavioral Predictors of Quality of Life Following Mild to Moderate Traumatic Brain Injury (Under Review). Schiehser, D.S., Matsevoyan, A.., Hanson, K.L., Lanni, E., Jak, A.J., Meloy, M.J., **& Delano-Wood, L.** Journal of Head Trauma and Rehabilitation.

Neuropsychology of Mild to Moderate TBI in OEF/OIF Veterans. (Under Review). Jak, A.J., Gregory, A., Orff, H.J., Colon, C., Steele, N., Schiehser, D., **Delano-Wood, L.,** & Twamley, E.W. Journal of the International Neuropsychological Society.

CONCLUSION

We continue to make considerable progress toward our stated goals as outlined in our Introduction above. Given greater collaborations with other VA TBI investigators, our laboratory has grown considerably and productivity has increased significantly. Collectively, my laboratory has completed several studies, 3 that our now published or in press, and another 5 that are expected to be under review by a peer-reviewed journal within the next few months. Recruitment continues at a solid pace, with another 36 participants scanned and tested in this past year. We expect to be especially productive this year and next as we continue to grow our lab while also rounding out our data collection so that we can then embark upon large-scale studies to test many of the hypotheses set forth in the original proposal.

REFERENCES

Sorg, S.F., **Delano-Wood, L.,** Schiehser, D.M., Luc, N., Hanson, K.L., Nation, D.A., Lanni, E., Jak, A.J., Lu, K., Meloy, M.J., Frank, L.R., & Bondi, M.W. (Under revised review). White matter integrity in veterans with mild traumatic brain injury: Associations with executive function and loss of consciousness. *Journal of Head Trauma and Rehabilitation.*

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Schiehser, D.M., Delis, D.C., Filoteo, J.V., **Delano-Wood, L.,** Han, S.D., Jak, A.J., Drake, A.I., & Bondi, M.W. (2011). Are self-reported symptoms of executive dysfunction associated with objective executive function performance following mild to moderate traumatic brain injury? *J Clin Exp Neuropsychol, 33(6), 704-14.*

APPENDIX

We list below publications and abstracts that were submitted since the start of the study.

White Matter Integrity in Veterans Mild Traumatic Brain Injury: Associations with Executive Function and Loss of Consciousness: A sample of carefully selected participants who displayed adequate effort, we have been able to show executive impairment in a subset of OEF/OIF veterans who have sustained mild to moderate TBI. These findings showed that, although there were no significant overall group differences between control and mTBI participants on DTI measures, a subgroup of mTBI participants with executive dysfunction demonstrated reduced white matter integrity of prefrontal white matter, corpus callosum, and cingulum bundle structures compared to mTBI participants without executive dysfunction. Interestingly, participants with TBI with loss of consciousness (LOC) were more likely to evidenced executive function difficulties and disrupted ventral prefrontal white matter integrity when compared to either TBI participants without LOC or control participants. Findings suggest that altered white matter integrity contributes to reduced executive functioning in subgroups of veterans with history of TBI and LOC may be a risk factor for reduced executive function as

Validation of the Modified Fatigue Impact Scale in Chronic Mild to Moderate Traumatic Brain Injury: (Dawn M. Schiehser, Lisa Delano-Wood, et al., In press, Journal of Head Trauma Rehabilitation). *Objective*: To evaluate the validity of the Modified Fatigue Impact Scale (MFIS) in a traumatic brain injury (TBI) military population. *Methods:* Participants were OEF/OIF/Gulf War veterans with a history of mild to moderate TBI (N = 106). Factor structure, internal consistency, convergent validity, sensitivity, and specificity of the MFIS were examined. The relationship between sample characteristics and the MFIS scores was also evaluated.*Results*: Principal Component Analysis identified two viable MFIS factors: a Cognitive subscale and a Physical subscale. Item analysis revealed high internal consistency of the MFIS Total scale and subscale items. Strong convergent validity of the MFIS scales was established with two Beck Depression Inventory (BDI-II) fatigue items. ROC analysis revealed good to excellent accuracy of the MFIS in classifying fatigued versus non-fatigued individuals. Furthermore, higher levels of overall and physical fatigue, but not cognitive fatigue, were associated with the presence of post-traumatic amnesia at injury. *Conclusion*: The MFIS is a valid multidimensional measure that can be used to evaluate cognitive and physical fatigue in individuals with mild to moderate TBI. Differences in the relationships between TBI characteristics and fatigue subtypes underscore the utility of a multidimensional fatigue scale in this population.

The Relationship between Post-Concussive Symptoms and Quality of Life in Veterans with Mild to Moderate TBI: (Schiehser D.M., Twamley E.W., Liu L., Matevosyan A., Filoteo J.V, Jak A.J., Orff H.J., Hanson K., & Delano-Wood L.) Objective: To assess the relationship between Quality of Life (QoL) and specific neurobehavioral symptoms in military veterans with mild to moderate postacute (>6 months) traumatic brain injury (TBI). *Methods:* Participants were 61 Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF)/Persian Gulf veterans with mild or moderate TBI and 21 demographically-matched military control participants. All participants were administered self-report measures of quality of life (QoL; World Health Organization Quality of Life -BREF) and neurobehavioral symptom severity (Neurobehavioral Symptom Inventory). *Results*: Veterans with mild to moderate TBI reported worse QoL compared to the control group. Affective symptoms best predicted Physical, Social, and Environmental QoL, with fatigue emerging as the only significant predictor. Depression, headache, sleep difficulty, attention problems, appetite changes, and irritability were significantly associated with specific areas of QoL.*Conclusion*: Specific neurobehavioral

symptoms are associated with different self-reported ratings of QoL in veterans with postacute mild to moderate TBI. Affective symptoms, and most predominantly fatigue, appear to be the most relevant neurobehavioral symptoms predicting postacute QoL. Our results have the potential to optimize targeted treatments to improve QoL in this vulnerable population.

Quantitative Tractography of the Fornix and Relationship to Working Memory in Veterans with Mild to Moderate Traumatic Brain Injury (in preparation) Lisa Delano-Wood,[4,1] Sorg, S.,[1,4] Schiehser, D.,[4,1] Luc, N.,[4] Clark, A.,[1,4] Lanni, E.,[4] Nation, D.,[4,1] Delis, D.C.,[1,4] & Frank, L.R.[3] *Objective:* White matter (WM) changes have been reported in mild TBI, although few diffusion tensor imaging (DTI) tractography studies of military personnel exist in the literature. This study investigated the fornix, a WM limbic structure that is particularly vulnerable to TBI-related diffuse axonal injury. Given this structure's connectivity and cholinergic input to the medial temporal lobe (MTL), we investigated associations between fornix microstructural integrity and cognition in both blast-related and mechanical blunt force mTBI. *Participants and Methods:* Seventy-three military veterans (mTBI: n = 53; NC: n = 20) were administered 3T DTI scans (61 directions) and a comprehensive neuropsychological evaluation. White matter tracking was employed by seeding ROIs in bilateral contiguous slices on a registered T1 image and mean DTI values were derived from individual fractional anisotropic (FA) and mean diffusivity (MD) maps. *Results:* The mTBI group performed significantly more poorly than NCs across several neuropsychological domains including attention/working memory, executive functioning, visual and verbal memory, and fine motor dexterity. Independent samples t-tests demonstrated that the mTBI group differed significantly from NCs on fornix FA (t = 3.00(71) t = $3.00_{[df= 71]}$, p = .004) as well as fornix MD (t = $-2.10_{[df= 71]}$, p = .038), but not on fornix volume (p = .22). Moreover, fornix DT indices positively correlated with performance on attention/working memory, executive functioning, and fine motor dexterity. Finally, mTBI subgroup analysis of blast, blunt, and NCs subgroups significantly differed on fornix MD (F = 3.47(75) = .036), fornix AD (F = 4.25(75), = .018), and trend with fornix RD (F = 2.74(75) = .07).

Iowa Gambling Task Impairment is Associated with Executive Dysfunction in Veterans with Chronic Mild to Moderate Traumatic Brain Injury: (Luc, N.K., Nation, D.A., Sorg, S.F., Schiehser, D.M., Hanson-Bondi, K.L., Bondi M.W., Lanni, E., Jak, A.J., Matsevoyan, A., Kim, R., Jacobson, M., & Delano-Wood L). *Objective:* The Iowa Gambling Task (IGT) has been widely employed to examine risk-related decision-making performance across several clinical populations; however, few studies have investigated performance on this task in the context of traumatic brain injury (TBI). Given that decision-making likely plays an important role in long-term functional outcome following neurotrauma, the current study compared IGT performance between OEF/OIF veterans with a history of chronic mild to moderate TBI and normal control (NC) participants. We hypothesized that mTBI patients would demonstrate deficits in decision-making and that IGT performance would be related to other measures of executive functioning. *Participants and Methods:* Forty-seven demographically-matched participants (TBI: n=26; NC n=21; mean age = 32.7; mean months since TBI = 80.7) were administered a comprehensive neuropsychological battery which included a computerized version of the IGT. Participants were divided into impaired and unimpaired performance on IGT based on a T-score cutoff corresponding to > 1 standard deviation below the mean ($T \leq 39$). *Results:* TBI participants were significantly more likely to exhibit impairment on the IGT total score relative to the NC group (% Impaired: TBI = 20.7%; NC = 0%; p = .02). Repeated measures ANOVA indicated a significant group by block interaction (p = .04), whereby the TBI group performed significantly worse than NCs on block 4 (p = .03) and were more likely to exhibit impairment on 2 or more blocks (% Impaired: TBI = 19.2%; NC = 0%). Collapsed across group, IGT performance was negatively related to executive functioning (DKEFS Trails Switching [r= -.36, p= .02], WCST Perseverative Responses [r= -.35, p=.02], and Set Losses [r -.30, p = .049]). *Conclusions:*

Findings indicate that mild to moderate military TBI is associated with subtle impairment in reward-related decision-making and suggest that the IGT may be a sensitive index of this aspect of executive dysfunction in military chronic TBI.

Relationships Between Effort, Psychiatric Symptom Reporting, and Structural Brain Changes in OEF/OIF Veterans with History of Mild TBI: (L. Clark, Scott F. Sorg, Mark W. Bondi, Norman Luc, Dawn M. Schiehser, Karen L. Hanson, Lawrence R. Frank, Amy J. Jak, James B. Lohr, & Lisa Delano-Wood). *Background:* Poor effort in the context of mild TBI (mTBI) is associated with inflation on symptom rating scales and decreased cognitive performance. Whether there are neurobiological abnormalities that underlie the clinical presentation of those who fail effort measures has not been studied. We therefore sought to further explore the role of effort and structural MRI brain in Veterans with and without history of mTBI. *Method:* 97 Veterans who underwent cognitive and 3T MRI assessments were divided into those with mTBI who passed (mTBI-P: n=52) and failed (mTBI-F: n=16) effort measures, and military controls (NCs: n=28) with no history of mTBI. Poor effort was defined by T1≤39 or T2<45 on TOMM or <15 on CVLT-Forced Choice. Mean cortical thickness was extracted from 6 frontal and temporal cortical ROIs; fractional anisotropy (FA) was extracted from 6 white matter (WM) ROIs. For the imaging analyses, the mTBI-P group was divided into those with intact executive function (EF) (mTBI-P+) and reduced EF (mTBI-P-). *Results:* The mTBI-F group endorsed greater psychiatric symptoms compared to mTBI-P (*p*'s<.002) and NC (all *p*'s<.001) groups. MANOVA revealed significant DTI differences across the 4 groups (Wilk's Lambda, p=.01); post hoc analyses revealed significantly decreased FA in the mTBI-P- group compared to all others. Overall FA means showed no significant differences between the mTBI-P+ group and mTBI-F group (p > .05); however, FA of the mTBI-F group fell between those of mTBI-P+ and mTBI-P-. A second MANOVA revealed no significant differences between groups on cortical thickness (p=.34). *Conclusions:* Findings show that mTBI patients with poor effort endorse significantly greater psychiatric symptoms compared to those with optimal effort, although DTI indices reveal that WM integrity in those with poor effort is intermediate between those TBI with intact vs. reduced cognition. Findings suggest mTBI participants with poor effort may represent a heterogeneous group composed of those with and without WM abnormalities.

Processing Speed and Memory Deficits in Veterans with Mild to Moderate TBI: Associations with Anterior White Matter Integrity: Scott Sorg, Lisa Delano-Wood, Dawn M. Schiehser, Norman Luc, Elisa Lanni, Amy J. Jak, Karen L. Hanson, M. J. Meloy, Daniel A. Nation, Mark Jacobson, Lawrence R. Frank, James Lohr, Mark W. Bondi. *Objective:* High rates of mild to moderate traumatic brain injuries (TBI) are reported in veterans of the Iraq and Afghanistan wars. The long-term neuropsychological outcome of these injuries and their relationship with cerebral white matter microstructure is unclear. Using diffusion tensor imaging (DTI) tractography, this study investigated the effects of TBI on a sample of veterans in terms of cognition and white matter integrity. *Participants and Methods:* Thirty-eight veterans with TBI and 17 veteran normal control (NC) participants completed neuropsychological and psychiatric testing with adequate effort and underwent a DTI scan an average of 4 years following their TBI event(s). Fractional anisotropy (FA), a measure of white matter integrity, was extracted from 7 white matter tracts. *Results:* TBI participants had higher depression and PTSD scores than the control group and completed fewer years of education. Controlling for age, education, depression, and PTSD symptoms, ANCOVA revealed that TBI participants performed worse than NCs on a memory composite (p=.02, η2=.11) and on a test of psychomotor processing speed (p=.02, η2=.11), whereas the two groups did not differ on an executive function composite (p=.37, η2=.02) or on a measure of attention (p=.56, η2=.01). The TBI group evidenced lower FA in the left cingulum bundle (p=.01, η2=.13) and in the genu of the corpus callosum (p=.03, η2=.09). Partial correlations adjusting for age and education showed significant positive

associations between psychomotor processing speed and FA in the left cingulum (r=.38, p=.04), genu (r=.50, p<.01) and body of the corpus callosum (r=.52, p<.01), and left posterior internal capsule (r=.45, p=.01). *Conclusions:* Results suggest that the cognitive consequences of TBI may be enduring in veterans, and may be associated with poorer performance in memory and processing speed. Findings further suggest that slowed processing speed may be a consequence of TBI-related damage to anterior white matter pathways.

Cognitive and Psychiatric Dissociations between Fractional Anisotropy and Cortical Thickness in Veterans with Mild TBI: (Scott Sorg, Mark W. Bondi , Dawn M. Schiehser, Norman Luc, Amy J. Jak, Alexandra Clark, Karen L. Hanson, James Lohr, Lisa Delano-Wood): *Objective:* Studies using diffusion tensor imaging (DTI) have shown lower white matter integrity in veterans with history of mild TBI (mTBI). However, the effect of mTBI on gray matter regions remains understudied in this population. Thus, in a sample of veterans with mTBI, we investigated the relationships among the cognitive effects of mTBI, PTSD symptom severity, and brain structure in terms of gray matter measured via cortical thickness (CT) and white matter integrity measured via fractional anisotropy (FA). *Participants and Methods:* Thirty-eight mild TBI and 17 normal control (NC) veteran participants completed neuropsychological and psychiatric testing (e.g., PTSD Check List) with adequate effort, and underwent MRI scanning an average of 4 years following their TBI event(s). Mean CT measures were extracted from 6 frontal and temporal cortical regions of interest and FA measures were extracted from 10 white matter tracts of interest.
Results: Adjusting for age, education, depression, and PTSD symptoms, mTBI participants performed worse than NCs on a memory composite and a test of psychomotor processing speed (p's<.05). CT did not differ between the mTBI and NC groups or correlate with cognitive test scores (p's>.05). Thinner left orbitofrontal CT was associated with higher PCL scores (p<.05). FA was lower in the TBI group than NCs in the left cingulum bundle (p<.05) and genu of the corpus callosum (p<.05). FA correlated with processing speed in seven tracts including the left cingulum (r=.38, p<.05) and genu (r=.50, p<.01). FA did not correlate with PCL scores (p>.05). Left cingulum bundle FA correlated with CT in the left middle frontal (r=.31, p<.05) and orbitofrontal cortices (r=.38, p<.01). *Conclusions:* Results demonstrated that gray matter thickness was associated with PTSD symptom severity but not cognition, whereas white matter anisotropy was associated with cognition but not PTSD symptom severity, suggesting dissociable neurobiologic substrates for the cognitive and psychological sequelae following mTBI.

The relationship between coping style, executive function, and mood in veterans with mild to moderate traumatic brain injury: (Kim, R., Delano-Wood, L., Delis, D.C., Lohr, J.B., Matevosyan, A., Hanson, K.L., Jak, A.J, Clark, A.L., & Schiehser, D.M.).
Objective: Preliminary evidence suggests that individuals with traumatic brain injury (TBI) may utilize maladaptive coping styles, such as avoidance or emotional (e.g., self-blame) coping, more than functional task-oriented/problem-solving coping styles, which in turn, can lead to poor psychological and functional outcome. Since executive dysfunction is frequently observed in veterans with history of TBI and may underlie reliance on less problem-focused coping styles, we sought to investigate the relationship between coping style, executive function, and mood in this population. *Participants and Methods:* Participants were Veterans (n = 20) with a history of mild to moderate TBI (6.9 mean years since injury) and Veteran controls (n = 18) without a history of TBI. All participants were administered measures of coping (Coping Inventory for Stressful Situations), executive function (Color-Word Interference Test; CWIT), effort (Test of Memory Malingering), depression, anxiety, and Post-Traumatic Stress Disorder (PTSD) symptoms.*Results:* Controlling for age, effort, depression, anxiety, and PTSD, TBI Veterans

reported significantly greater usage of Avoidance coping compared to controls (p = .03); groups did not differ in their use of Task-Oriented or Emotional coping (all p's > .62). In the TBI group, Avoidance coping was significantly associated with worse CWIT Inhibition/Switching (p = .02), but was not related to depression, anxiety, or PTSD (all p's > .56). *Conclusions:* Reduced executive function is strongly associated with greater usage of a maladaptive avoidance coping style in Veterans with history of mild to moderate TBI; use of avoidance coping cannot be explained by mood, PTSD symptoms or effort. These findings suggest that proper assessment and targeted cognitive interventions that focus on executive dysfunction may improve coping and long-term outcomes in this population.

Poor Effort is Associated with Increased Reporting of Injury Characteristics and Postconcussive Symptomatology but not Structural Brain Changes: A Multidisciplinary Study of OEF/OIF Veterans with History of Mild TBI. (Alexandra L. Clark, Scott Sorg, Mark W. Bondi, Norman Luc, Dawn Schiehser, Karen Hanson, Dean C. Delis, Lawrence Frank, Amy J. Jak, James Lohr, & Lisa Delano-Wood) *Background:* Studies investigating the role of effort in OEF/OIF Veterans with history of mild TBI (mTBI) have generally shown that poor effort is strongly associated with inflation on symptom rating scales, increased rates of clinical diagnoses, and decreased neurocognitive test performance. However, whether there are neurobiological abnormalities that underlie this pattern of increased symptom endorsement and clinical presentation in those who fail effort measures has not been studied. Therefore, the current study sought to explore the relationship between effort, symptom reporting, and structural brain changes (Freesurfer-derived values of cortical thickness and indices of white matter integrity using DTI) in OEF/OIF veterans with history of mTBI. *Method:* Ninety-seven (83M/14F) OEF/OIF Veterans (mean age = 31; mean time since injury = 2.3 years) underwent neuropsychological assessment and 3T MRI scanning. Participants were divided into those with history of mTBI who passed effort measures (mTBI-Pass: n = 52), those with mTBI who failed effort measures (mTBI-Fail: n = 16), and military combat controls (NC: n = 28) with no history of mTBI. Poor effort was defined by failure on the Test of Memory Malingering (TOMM) (Trial 1 score < 45) or CVLT Forced Choice Recognition (total score < 15)..Mean cortical thickness measures were extracted from 6 frontal and temporal cortical regions of interest and FA measures were extracted from 10 white matter tracts of interests. *Results:* Collapsed across effort, when compared to the NCs, the overall mTBI group showed significantly elevated scores on measures of PTSD (p = .001), depression (p = .01), and anxiety (p = .015). Within the mTBI group, in comparison to the mTBI-Pass subgroup, the mTBI-Fail subgroup reported less time since their most recent TBI (p = .03) and higher levels on all psychiatric measures (PTSD, depression, and anxiety; all p-values < .002). Additionally, the mTBI-Fail subgroup reported significantly more severe injury characteristics (LOC, AOC, PTA; all p-values < .05) and increased postconcussive severity (p < .015) in the context of reduced performance across multiple cognitive domains measured (all p-values < .05). However, although the overall mTBI group showed greater white matter and cortical thickness abnormalities when compared to NCs, there were no significant differences between the mTBI-Pass and mTBI-Fail groups on any of the imaging indices examined. *Conclusions:* Despite considerably elevated subjective complaints, injury severity reporting, and symptom endorsement in those with mTBI with low vs. high effort results of this study show that, in our cohort of mTBI veterans with poor effort, there are no objective gray or white matter differences –above and beyond those attributable to mTBI—that might explain this pattern of exaggerated injury and symptom reporting. Future research focusing on symptom attribution and illness perception may aid in understanding more about the relationship between reduced effort and increased symptom endorsement patterns following neurotrauma in this vulnerable population.

Alcohol Misuse is Associated with Increased Psychiatric Symptomatology and Reduced Processing Speed in Veterans with Mild Traumatic Brain Injury. (Karen L. Hanson, Ph.D., Dawn M. Schiehser, Ph.D., Elizabeth Twamley, Ph.D., Amy J. Jak, Ph.D., Alexandra L. Clark, B.A. , James B. Lohr, Ph.D. Dean C. Delis, Ph.D. & Lisa Delano-Wood, Ph.D.) *Introduction:* Given that little is known about the role of alcohol misuse in the cognitive and psychiatric outcomes among veterans with mild traumatic brain injury (mTBI), we aimed to: (1) characterize how veterans with mTBI differ from military combat controls on measures of alcohol misuse, psychiatric symptomatology, and cognition; (2) determine the risk factors for problematic alcohol use among veterans with mTBI; and (3) examine whether problematic alcohol use is associated with increased psychiatric symptoms and reduced cognition among veterans with mTBI. *Methods:* 77 veterans (n=48 with mTBI history; n=29 veteran combat normal controls [NCs]; mean age = 31.9; 14% women) completed an assessment of problematic alcohol use (Alcohol Use Disorders Identification Test: AUDIT), psychiatric symptoms, and neuropsychological (NP) functioning. Participants who reported current (within 30 days) alcohol or substance dependence (DSM-IV criteria) or a positive toxicology screen taken on the day of testing were excluded from the study. Only participants who demonstrated optimal effort (64/77) upon testing were included in the cognitive analyses. *Results:* Compared to NCs, there was a trend revealing that the mTBI group was more likely to score above the AUDIT cut-off score of 8 (p=.066). Within the mTBI group, higher AUDIT scores correlated with younger age at testing (r= -.45, p=.001) and lower education (r=-.30, p=.007), as well as the following injury characteristic variables: younger age at last TBI (rho=-.38, p=.01), shorter (?) post-traumatic amnesia duration (rho=-.60, p=.001), and increased blast-related quaternary effects (*rho*=.45, p=.019). When compared to the mTBI group with low AUDIT scores, the mTBI group scoring above the AUDIT cutoff reported higher levels of depression(p=.005) and anxiety (p=.02), and increased neurobehavioral symptoms (p=.026)), but there were no differences on PTSD symptoms p = .11). Finally, higher AUDIT scores were associated with slower visuomotor processing speed (p = .02) but not other NP domains. *Conclusion:* Findings suggest that (1) compared to NCs, mTBI veterans are more likely to report alcohol-related problems, (2) younger and less educated mTBI veterans appear to be at higher risk for alcohol misuse (abuse?), and (3) alcohol misuse among mTBI veterans is associated with elevated psychiatric symptoms and slower visuomotor processing speed. These results emphasize the importance of assessing for and treating problematic alcohol use among veterans with history of neurotrauma.

Visual but not Verbal Memory Performance is Impaired in Veterans with Chronic Mild to Moderate TBI. **(**Adelina Matevosyan, Lisa Delano-Wood, Omar Alhassoon, Karen Hanson, Elisa B. Lanni, Norman Luc, Russell Kim, & Dawn M. Schiehser) *Objective:* Memory impairments have been documented in individuals with acute mild to moderate traumatic brain injury (TBI), and there is some evidence of faster recovery of verbal compared to visual abilities post-injury. However, few studies have examined differences between material-specific memory in a chronic TBI sample of military veterans. We thus investigated potential differences in performance on both verbal and visual material-specific memory tasks in individuals with chronic TBI compared to demographically-comparable normal control participants. *Method:* Thirty veterans with a history of TBI (mean age=32.2, mean months since injury=78.33) and 26 demographically-matched normal controls (NCs) (mean age=33.3) were administered the Logical Memory (LM) and Visual Reproduction (VR) subtests from the Wechsler Memory Scale, version four (WMS-IV). *Results:* A one-way MANOVA revealed a significant multivariate main effect between the groups, Wilks' λ = .798, ($F_{(4,51)}$ = 3.23, p =.019, ηp^2=.202) with the TBI group performing worse on all memory tasks than NCs. Significant univariate main effects were found in immediate visual memory ($F_{(1,54)}$=8.51, p=.005, ηp^2=.136) and marginally significant effects were found in delayed visual memory ($F_{(1,54)}$=3.782, p=.057, ηp^2=.065). Performance in verbal memory did not significantly differ between groups (all p-values >.05).

Conclusion(s): Findings revealed that in a chronic mild-moderate TBI sample of military veterans, visual memory but not verbal memory was significantly compromised compared to control participants. Results indicate that memory impairments in chronic TBI may be material-specific, and they underscore a need for comprehensive systematic neuropsychological screening and modality-specific treatment in this vulnerable population.

Correlates of TBI History in Aging Veterans Presenting with Cognitive Difficulties: A Clinical Case Series: (Nation, D.A., Abuyo, T., Delano-Wood, L., Jak, A.J., Bondi, M.W. Objective) We sought to investigate the relationship between cognitive aging and history of traumatic brain injury (TBI) among aging veterans in order to further our understanding of the interaction between TBI and age-related cognitive disorders. *Methods:* A case series of 104 Veterans (age mean=70.5, range=46-89; 94.2% male) referred for neuropsychological evaluation of cognitive difficulties (self- or informant-report) were compared on demographics, cognition, and psychiatric history based on whether there was history of TBI (n=54) or not (n=50). No participants were referred because of a known TBI, but history of TBI was assessed during clinical interview and chart review. Analyses were performed across the entire sample and after stratification by clinical diagnosis [normal cognition, Cognitive Disorder, or Dementia]. The main effects of TBI history and the interaction of TBI history with clinical diagnoses were evaluated by ANOVA. Chi-square analyses compared rates of anxiety, depression, PTSD, and alcohol/substance abuse history. *Results:* There was a main effect of TBI history on age at presentation, such that Veterans with a history of TBI were younger than those without a history of TBI (p=.001). Veterans with a history of TBI were also more likely to have a history of anxiety (p=.01) and PTSD (p=.026), but were no more likely to exhibit depression or alcohol/substance abuse. There were no differences in dementia rating scale scores. *Conclusions:* Among middle- to older-age Veterans presenting with cognitive difficulties, those with an incidentally discovered history of TBI tended to be younger, potentially suggesting that TBI could influence the age at which cognitive difficulties emerge. Those with a history of TBI were also more likely to have histories of mood and anxiety disorders, suggesting psychiatric factors may play a role in the interaction between cognitive aging and TBI.

Validation of the Modified Fatigue Impact Scale in Mild to Moderate Traumatic Brain Injury

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Objective: To evaluate the validity of the Modified Fatigue Impact Scale (MFIS) in veterans with a history of mild to moderate traumatic brain injury (TBI). **Participants:** Veterans ($N = 106$) with mild (92%) or moderate (8%) TBI. **Setting:** Veterans Administration Health System. **Procedure:** Factor structure, internal consistency, convergent validity, sensitivity, and specificity of the MFIS were examined. **Results:** Principal component analysis identified 2 viable MFIS factors: a Cognitive subscale and a Physical/Activities subscale. Item analysis revealed high internal consistency of the MFIS Total scale and subscale items. Strong convergent validity of the MFIS scales was established with 2 Beck Depression Inventory II fatigue items. Receiver operating characteristic curve analysis revealed good to excellent accuracy of the MFIS in classifying fatigued versus nonfatigued individuals. **Conclusion:** The MFIS is a valid multidimensional measure that can be used to evaluate the impact of fatigue on cognitive and physical functioning in individuals with mild to moderate TBI. The psychometric properties of the MFIS make it useful for evaluating fatigue and provide the potential for improving research on fatigue in this population. **Key words:** *assessment*, *fatigue*, *Modified Fatigue Impact Scale*, *traumatic brain injury*, *validity*

FATIGUE IS A COMMON and disabling problem after traumatic brain injury (TBI).[1–4] It is estimated that 50% to 77% of individuals with TBI experience postconcussive fatigue,[5,6] and fatigue is reported to be one of the symptoms most often endorsed by individuals with TBI.[7] Moreover, approximately 50% of patients with TBI identify fatigue as one of their worst or most distressing symptoms.[8]

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While there is no universally accepted definition of fatigue, it has frequently been conceptualized as a multidimensional construct characterized by "extreme and persistent tiredness, weakness or exhaustion–mental, physical or both."[9(p157)] There is no criterion standard for measuring fatigue, but the most prevalent method is by self-report rating instruments. While a large number of subjective fatigue scales have been developed, at the present time, no single valid and reliable measure exists.[10] Two of the questionnaires most often used with individuals with TBI are the Fatigue Impact Scale (FIS)[11] and the Fatigue Severity Scale (FSS).[12,13] These 2 scales differ conceptually. The FSS is a unidimensional 9-item measure that assesses how fatigue affects a person's functioning *in general*, whereas the FIS is a 40-item multidimensional instrument designed to measure how fatigue affects *specific* aspects of physical, cognitive, and psychosocial functioning. In a recent review of fatigue scales, the FIS and FSS were identified as 2 of only 3 short instruments with demonstrably good psychometric properties.[14] Ziino and Ponsford evaluated the FSS in addition to 2 other subjective fatigue scales, the Visual Analogue Scale for Fatigue[15] and the Causes of Fatigue Questionnaire,[1] in individuals with mild to severe TBI and found that the FSS was sensitive to fatigue in TBI whereas the Visual Analogue Scale for Fatigue could not differentiate the

TBI group from controls.[1] When the FSS was compared with the Visual Analogue Scale for Fatigue and the FIS in a mixed sample (eg, fall, assault, stroke, aneurysm) of individuals with chronic symptoms of fatigue following brain injury (mean = 44 months since injury), the FIS provided the most comprehensive examination of fatigue, given its ability to distinguish those with brain injury from a control group, as well as its significant correlation with an objective measure of fatigue.[8] While both the FIS and the FSS have demonstrated utility in TBI, the FIS may be the most comprehensive, and therefore clinically useful, scale. As the FIS measures separate dimensions of fatigue, using this scale with TBI populations may be advantageous.

One clinical drawback of the FIS, however, is its length, and patients–particularly those with a history of head injury–may have difficulty concentrating on and completing all items.[8] Therefore, the 40-item FIS was truncated to 21 items, while retaining its comprehensive examination of fatigue, and renamed the Modified Fatigue Impact Scale (MFIS). The MFIS purportedly retains the 3 subscales (ie, Physical, Cognitive, and Psychosocial) of the original FIS. The Multiple Sclerosis Council for Clinical Practice Guidelines recommends the MFIS for use in clinical practice and research,[16] and empirical studies have supported the utility of the MFIS in individuals with multiple sclerosis[17] and Parkinson disease.[18] While a recent study has shown that the MFIS was the best predictor of disability status in chronic TBI,[19] to our knowledge, no psychometric studies of the MFIS in TBI currently exist. Examining the psychometric properties of the MFIS in TBI is important for researchers and clinicians who may wish to use this scale to evaluate, monitor, and treat individuals with TBI and fatigue.

The aim of this study was to evaluate the utility of the MFIS in a sample of veterans with a history of mild to moderate TBI by examining the factor structure, sensitivity and specificity of the scale, internal consistency of the scale items, and convergent validity with fatigue-related items from another measure. On the basis of the information from the published scale,[16] we predicted a similar 3-factor structure of the MFIS representing the impact of fatigue on physical, cognitive, and psychosocial functioning. We further predicted high internal consistency of the items and adequate convergent validity and sensitivity/specificity with the Beck Depression Inventory II (BDI-II) items that inquire about fatigue.

METHODS

Participants

Participants were 106 Operation Enduring Freedom/Operation Iraqi Freedom/Persian Gulf veterans with a history of mild to moderate TBI. A TBI is defined by the Veterans Administration/Department of Defense clinical practice guideline for management of concussion/mild TBI as "a traumatically induced structural injury and/or physiologic disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least *one* of the following: (1) any period of loss of consciousness (LOC); (2) any loss of memory for events immediately before or after the accident (posttraumatic amnesia; PTA); (3) any alteration in mental state at the time of the accident (alteration of consciousness; AOC); or (4) neurological deficits that may or may not be transient." Ninety-seven participants (92% of total sample) met criteria for a *mild TBI* defined by (*a*) an initial LOC shorter than 30 minutes, (*b*) AOC up to 24 hours, (*c*) an initial Glasgow Coma Scale (GCS) score between 13 and 15, and/or (*d*) PTA of less than 24 hours." Nine participants (8% of sample) met criteria for a *moderate* TBI defined by (*a*) an initial LOC between 30 minutes and 24 hours, (*b*) AOC greater than 24 hours, (*c*) an initial GCS score between 9 and 12, and/or (*d*) PTA duration greater than 24 hours but less than 7 days.[20] As is common in retrospective studies of military personnel, medical records regarding length of LOC/AOC, GCS scores, and PTA were often unavailable, so information was frequently obtained by patient self-report. For these reasons, we were unable to report mean LOC and PTA duration for all participants (see "Limitations" later). No GCS scores were available for this study. Information was gathered regarding the participants' self-described "worst" or "most significant" TBI, and self-reported LOC and PTA duration was used to determine injury severity. For their most significant TBI, 74% of the TBI participants ($n = 78$) sustained a blast injury with ($n = 14$) or without ($n = 47$) a secondary blunt or unknown blunt ($n = 17$) injury; 26% ($n = 28$) sustained a blunt injury (eg, motor vehicle accident, fall).

Exclusion criteria included (1) a history of severe head injuries defined by an initial LOC more than 24 hours and/or PTA duration more than 7 days; (2) any current or past substance or alcohol abuse/dependence according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition), criteria; (3) a history of another neurological or metabolic disorder or other diseases known to affect the central nervous system; or (4) a history of bipolar disorder, schizophrenia, or other psychotic disorders. All participants were recruited from the Veterans Affairs San Diego Healthcare System. This study was approved by the local institutional review board committee. Table 1 provides demographic and injury characteristics.

Materials and procedure

All patients were administered the MFIS as part of a comprehensive neuropsychological evaluation. The

TABLE 1 *Demographic and injury severity characteristics*

Age, mean (SD), y	32.2 (7.6) (range = 22-61)
Education, mean (SD), y	13.9 (1.6) (range = 10-20)
Gender (male:female)	101 (95.3%):5 (4.7%)
Time since TBI, mean (SD), mo	76.5 (43.3) (range = 6-280)
TBI severity (mild:moderate)	97 (91.5%):9 (8.5%)
TBI type	
Blunt	26.4%
Blast/no secondary injury	44.3%
Blast + secondary blunt injury	13.2%
Blast/unknown secondary injury	16.0%
LOC/AOC	
+LOC	67.9%
+AOC (no LOC)	32.1%
LOC, mean (SD),[a] min	23.0 (96.1) (range = 0.05-720)
Posttraumatic amnesia	
Yes	44.3%
No	31.1%
Undetermined	24.5%

Abbreviations: AOC, alteration of consciousness; LOC, level of consciousness.
[a] $n = 68$; LOC duration of 4 of the 72 subjects who endorsed + LOC could not be determined.

MFIS measures the impact of fatigue on functioning by having participants rate how often fatigue has affected 21 functions during the past 4 weeks using a 0 (*never*) to 4-point (*almost always*) scale. Scores range from 0 to 84, with higher scores indicating greater impact of fatigue. According to the original published guidelines, the items can be aggregated into a total score (21 items) as well as 3 subscales: Physical (9 items; eg, "been physically uncomfortable"), Cognitive (10 items; eg, "been less alert"), and Psychosocial (2 items; eg, "been less motivated to participate in social activities"). To evaluate convergent validity, the MFIS Total and subscale scores were compared with the sum of the fatigue items (#15: Loss of Energy and #20: Tiredness or Fatigue) of the BDI-II.[21]

Statistical analyses

To evaluate the underlying structure of the MFIS, individual scores were subjected to a principal component analysis (PCA) with varimax rotation. The Cronbach α was used to examine the internal consistency of the 21 total items and items within the subscales identified in the PCA. To examine convergent validity, Spearman rank correlations were used to correlate the MFIS with the sum of the BDI-II fatigue items. Significant correlation coefficients that were greater than 0.5 were interpreted as strong, coefficients of 0.3 to 0.5 were interpreted as moderate, and coefficients less than 0.3 were interpreted as weak.[22] Sensitivity and specificity were examined using a receiver operating characteristic curve analysis to assess the accuracy of the MFIS in discriminating between the fatigued and nonfatigued groups using the BDI-II fatigue item score (item #20; dichotomized as 0 = fatigued; ≥ 1 = nonfatigued) that most specifically addresses fatigue. All analyses used a sample size of 106, unless otherwise indicated.

RESULTS

MFIS factor structure, item analysis, and convergent validity

To confirm the construct validity of the 3 MFIS subscales representing cognitive, physical, and psychosocial fatigue, a PCA with varimax rotation was computed. Two factors with eigenvalues greater than 1.0 were extracted. After rotation, these 2 interpretable factors, which we term "Cognitive" and "Physical/Activities," explained 35.4% and 33.0% of the variance, respectively. Eleven items loaded on the Cognitive subscale and 10 items loaded on the Physical/Activities subscale. All items clearly loaded onto one factor versus the other, with the exception of the 12th item ("Mental motivation"), which had a loading of 0.597 on the Cognitive factor and 0.516 on the Physical/Activities factor (see Table 2). All items also met the Hair et al[23] recommended cutoff of 0.55 for a sample size of 100, with the exception of the first item ("Alertness"), which had a loading of 0.480 on the Cognitive factor. A sensitivity analysis excluding items 1 and 12 in a factor analysis revealed that the factor structure did not change.

Item analysis using the Cronbach α suggested high internal consistency of all 21 items and the items within the 2 PCA-identified subscales, with an overall Cronbach α of 0.97 for all 21 items, 0.95 for the 11 items (including items 1 and 12) of the Cognitive subscale, and 0.96 for the 10 items of the Physical/Activities subscale. No item had a score higher than the overall α. An item analysis without items 1 and 12 was also performed, revealing that exclusion of these items did not significantly change the overall α (0.97) or the Cognitive subscale α (0.95). Means and standard deviations for each MFIS item are presented in Table 2. Convergent validity, as measured by the

TABLE 2 *Item means (standard deviations) and factors derived from principal component analysis with varimax rotation*[a]

Item	Description	Mean (SD)	Factor	
			Cognitive	Physical/Activities
1	Alertness	1.52 (1.2)	**0.480**	0.247
2	Attention	2.53 (1.1)	**0.752**	0.355
3	Clear thinking	2.15 (1.2)	**0.759**	0.328
4	Coordination	1.63 (1.2)	**0.628**	0.365
5	Forgetfulness	2.63 (1.2)	**0.660**	0.395
11	Decision making	1.94 (1.3)	**0.678**	0.505
15	Mental task completion	1.85 (1.2)	**0.789**	0.346
16	Thought organization	2.11 (1.4)	**0.793**	0.274
18	Slowed thinking	1.94 (1.3)	**0.766**	0.304
19	Concentration	2.40 (1.3)	**0.869**	0.358
12	Mental motivation	1.78 (1.3)	*0.597*	0.516
6	Physical activity pace	1.84 (1.3)	0.374	**0.708**
7	Physical motivation	2.05 (1.3)	0.302	**0.792**
8	Social motivation	2.36 (1.3)	0.411	**0.697**
9	Outside activity limitation	1.77 (1.3)	0.390	**0.774**
10	Physical effort maintenance	1.82 (1.3)	0.395	**0.802**
13	Muscle weakness	1.73 (1.3)	0.379	**0.771**
14	Physical comfort	1.97 (1.3)	0.338	**0.759**
17	Physical task completion	1.44 (1.3)	0.375	**0.773**
20	Physical activity limitation	1.58 (1.4)	0.304	**0.814**
21	Need for rest	1.77 (1.3)	0.359	**0.786**

Bold values represent highest significant factor loadings; italics values represent highest trend factor loadings.
[a]Item description does not reflect the Modified Fatigue Impact Scale item text in its entirety. Range for all items was 0 to 4.

correlation between the MFIS Total and subscale scores and the BDI-II fatigue items, was strong (all $r_s > 0.63$, $P < .001$) (see Table 3).

Sensitivity and specificity

Using the dichotomized BDI-II fatigue item (#20), 81 of the participants with TBI (76.4%) were classified as "fatigued" and 25 (23.6%) were classified as "nonfatigued". The receiver operating characteristic curve analysis revealed that the area under the curve (AUC) was 0.899 (95% confidence interval, 0.840-0.958) for the MFIS Total score, suggesting that the MFIS had good to excellent accuracy in classifying fatigued versus nonfatigued participants. The AUC was 0.858 (95% confidence interval, 0.784-0.931) for the Cognitive subscale and 0.888 (95% CI, 0.827-0.950) for the Physical/Activities subscale. Sensitivity and specificity analyses revealed optimal MFIS Total, Cognitive, and Physical/Activities cutoff scores of 29.0, 18.5, and 14.5, respectively. Sensitivity, specificity, cutoff scores, and the AUC for the MFIS Total and subscales are presented in Table 4.

TABLE 3 *Means (standard deviations) and correlations between MFIS scores and BDI-II aggregated fatigue items*

	Mean (SD)	Fatigue BDI-II
MFIS Total score	40.83 (11.5)	0.72[a]
MFIS Cognitive	22.49 (11.2)	0.63[a]
MFIS Physical/Activities	18.3 (11.5)	0.71[a]

Abbreviations: BDI-II, Beck Depression Inventory II; Fatigue BDI-II, BDI-II aggregated items 15 and 20; MFIS, Modified Fatigue Impact Scale.
[a]$P < .001$.

DISCUSSION

This study revealed that, in contrast to the original scale that comprised 3 subscales, the factor structure of the MFIS in a mild to moderate TBI sample consisted of 2 subscales, "Cognitive" and "Physical/Activities." The former "Psychosocial" subscale items were found to unequivocally load on this study's "Physical/Activities" factor. All other items loaded onto the original factors, with the exception of item 4 ("Coordination"), which loaded onto the "Cognitive" factor instead of the

TABLE 4 *ROC analysis: Optimal sensitivity, specificity, cutoff scores, and area under the curve for the MFIS Total and subscale scores*

Scale	Sensitivity	Specificity	Cutoff score	ROC area
MFIS Total	0.864	0.720	27.5	0.899
	0.852	**0.800**	**29.0**	
	0.840	0.800	31.0	
MFIS Cognitive	0.852	0.600	17.5	0.858
	0.827	**0.680**	**18.5**	
	0.753	0.680	19.5	
MFIS Physical/Activities	0.827	0.840	13.0	0.888
	0.815	**0.920**	**14.5**	
	0.802	0.920	15.5	

Abbreviations: MFIS, Modified Fatigue Impact Scale; ROC, receiver operating characteristic.
Bold values represent cut-off scores with the best balance between sensitivity and specificity.

original "Physical" factor, and item 12 ("Mental motivation"), which was too ambiguous to statistically attribute to one specific factor, yet had a higher loading on the Cognitive subscale. Item 1 ("Alertness") did not meet the Hair et al[23] criteria for inclusion, but it revealed a higher factor loading onto the Cognitive subscale. Including or excluding items 1 and 12 did not significantly alter the integrity of the overall scale or the Cognitive subscale, suggesting that including these items is not problematic.

The finding of 2, rather than 3, MFIS subscales was reported in a recent study of patients with Parkinson disease.[18] However, in this study, item 1 was ambiguous, albeit it loaded higher on the Cognitive factor, item 4 ("Coordination") loaded on the Physical factor, and item 12 ("Mental Motivation") loaded on the Cognitive factor. Although 2 items in the original scale were reported to measure psychosocial aspects of fatigue ("Social motivation" and "Outside activity limitation"), the results of this study, as well as those of Schiehser et al,[18] suggest that these items are related to physical fatigue rather than a separate psychosocial domain. Interestingly, coordination/clumsiness did not load on the Physical/Activities subscale but rather on the Cognitive subscale. As many neurological diseases and disorders can affect motor coordination, this finding suggests that cognitive fatigue may play a role in motor coordination in neurological populations, such as TBI.

This study revealed that the MFIS had a strong association with the 2 BDI-II fatigue-related items, indicating strong convergent validity of the scale. Furthermore, the MFIS Total score and each of the subscales were highly accurate in classifying fatigued versus nonfatigued individuals. Optimizing both sensitivity and specificity, results suggest that using a cutoff of 29.0 for the MFIS Total score may differentiate fatigued versus nonfatigued individuals with mild to moderate TBI. Furthermore, a cutoff score of 18.5 and 14.5 for the Cognitive and Physical/Activities subscales, respectively, may also be useful.

To our knowledge, this study represents the first to statistically evaluate the validity of the MFIS in a TBI population. Our findings revealed that the MFIS best reflects 2 subscales that measure cognitive and physical fatigue and that this modified scale demonstrates high internal consistency and strong convergent validity with fatigue items from another commonly used measure. Limitations of this study include the ability to generalize the results to severe TBI or civilian populations as well as TBI characteristics (LOC, PTA) obtained by self-report, although the latter is often the only way to obtain this information in TBI populations. In addition, the dichotomized fatigue item (#20) from the BDI-II was used to measure sensitivity and specificity and establishing optimal cutoff scores. Although there is no established criterion standard measure of fatigue, the use of a more robust measure of fatigue may be beneficial to corroborate and extend our findings.

In conclusion, this study demonstrates that the MFIS is a valid multidimensional measure that can be used to evaluate the impact of fatigue on cognitive and physical functioning in individuals with mild to moderate TBI. It also provides the potential for advancing clinical care as well as improving research focusing on fatigue in this vulnerable population.

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White Matter Integrity in Veterans With Mild Traumatic Brain Injury: Associations With Executive Function and Loss of Consciousness

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Objective: We investigated using diffusion tensor imaging (DTI) the association between white matter integrity and executive function (EF) performance in postacute mild traumatic brain injury (mTBI). In addition, we examined whether injury severity, as measured by loss of consciousness (LOC) versus alterations in consciousness (AOC), is related to white matter microstructural alterations and neuropsychological outcome. **Participants:** Thirty Iraq and Afghanistan War era veterans with a history of mTBI and 15 healthy veteran control participants. **Results:** There were no significant overall group differences between control and mTBI participants on DTI measures. However, a subgroup of mTBI participants with EF decrements ($n = 13$) demonstrated significantly decreased fractional anisotropy of prefrontal white matter, corpus callosum, and cingulum bundle structures compared with mTBI participants without EF decrements ($n = 17$) and control participants. Participants having mTBI with LOC were more likely to evidence reduced EF performances and disrupted ventral prefrontal white matter integrity when compared with either mTBI participants without LOC or control participants. **Conclusions:** Findings suggest that altered white matter integrity contributes to reduced EF in subgroups of veterans with a history of mTBI and that LOC may be a risk factor for reduced EF as well as associated changes to ventral prefrontal white matter. **Key words:** *diffusion tensor imaging*, *executive functions*, *traumatic brain injury*, *white matter*

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MILD TRAUMATIC BRAIN INJURY (mTBI) is common among Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans, with estimated prevalence rates ranging from 15% to 30%.[1,2] Despite these high rates, the long-term neuropsychological consequences of mTBI in this population are not well defined. Deficits in processing speed, attention, working memory, memory, and executive functions (EFs) have been frequently demonstrated in the acute phase following mTBI[3,4]; however, the prevalence and severity of cognitive deficits in the postacute phase (ie, after 3-6 months) are much less clear. Although there are reports showing chronic neuropsychological difficulties following mTBI,[5–7] meta-analytic

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studies using unselected and prospective samples report only transient impairments in multiple cognitive domains that tend to return to the normal range by 3 months postinjury.[8–11] However, when studies using clinical samples (ie, self-referred and/or with persisting cognitive complaints) are included, mTBI has a medium to large effect on neuropsychological functioning in the postacute phase.[12,13] Those factors that relate to enduring postacute symptomatology remain elusive, although some studies have shown associations with injury severity as well as confounding psychiatric conditions such as depression and anxiety.[6,14–16] In addition, problems associated with effort and litigation have also been implicated.[12,17]

As suggested by the aforementioned meta-analyses,[8–11] any long-term effects of mTBI, if present, are likely subtle. Given these suggestions coupled with the well-documented finding that the structural vulnerability of the frontal lobes in TBI may contribute to impaired EF performance,[18–20] it may be that mTBI preferentially affect specific higher-order cognitive skills such as EF that rely on the integration of multiple component cognitive processes. In support of this possibility, a meta-analysis by Rohling et al[10] reported that, although the overall effect of mTBI was negligible after 3 months, a small but significant decrement remained in the working memory domain. In addition, Hartikainen et al[21] reported that protracted recovery following mild to moderate TBI was associated with poorer performance measures of EF. Finally, Vanderploeg et al[22] found indications of executive dysfunction in the form of heightened proactive interference in US military personnel 8 years post-mTBI, and Nolin[23] has reported deficient encoding strategies in mTBI.

The high prevalence of mTBI in OEF/OIF veterans underscores the need for improved understanding of its possible long-term cognitive consequences, its underlying brain changes, and for enhanced characterization of those factors that may contribute to poorer outcomes. White matter is particularly vulnerable to the effects of the shearing and stretching forces characteristic of neurotrauma, and some studies using diffusion tensor imaging (DTI) have found evidence for disrupted white matter integrity following mTBI.[24–30] Diffusion tensor imaging is a noninvasive neuroimaging method used to investigate and characterize the microstructural integrity of the white matter.[31] Specifically, DTI allows for in vivo examination of the orientation of the white matter by reflecting the degree of intravoxel diffusion anisotropy, most commonly represented as fractional anisotropy (FA).[32,33]

Importantly, a decrease in FA within a structure suggests a disruption of the microstructure and possible tissue damage.[32] Such reductions in FA may result from a decrease in axial diffusivity (AD) (diffusion along the principal diffusion direction [along the axon]), an increase in radial diffusivity (diffusion perpendicular to the primary diffusion direction), or an additive or synergistic effect of the two. Although there is some debate as to the specific meaning of the component diffusion measures,[34,35] AD has most commonly been interpreted as describing axonal integrity, and radial diffusivity (RD) has been described as a proxy for myelin integrity.[36]

Injury characteristics such as loss of consciousness (LOC) are used to assign the severity of injury as "mild," although they have often been shown to be unrelated to cognitive outcomes within mTBI samples.[37] Among OEF/OIF veterans who have experienced a TBI, the distinction between LOC versus an altered state of consciousness (AOC)–but without LOC–following a head injury has been a focus of recent research.[1,38–40] However, it remains unclear to what degree these potential differences in severity within mTBI are associated with outcome, and the neuropsychological consequences of LOC versus AOC in the context of military TBI have not been fully explored.

The goals of the current study were to (1) assess whether OEF/OIF veterans with a history of mTBI demonstrate alterations in white matter microstructure; (2) determine whether our mTBI sample shows EF decrements; (3) investigate the extent to which executive dysfunction is associated with frontal white matter alterations; and (4) in an exploratory analysis, examine whether injury severity as indexed by LOC is associated with white matter damage and concomitant executive dysfunction. Given prior discrepant findings across studies of chronic mTBI, we did not expect our overall sample of chronic mTBI participants to show gross alterations in white matter microstructure or cognitive dysfunction relative to healthy control participants; however, a subgroup of mTBI participants with evidence suggestive of cognitive dysfunction was expected to show poorer white matter microstructural integrity. We also examined whether and how differences in AD or RD explain any significant subgroup differences in white matter integrity in terms of axonal or myelin compromise. Finally, in an exploratory analysis, we posited that mTBI participants with LOC (vs those with AOC) would evidence poorer white matter integrity, particularly in anterior regions.

METHODS

Participants

Forty-five OIF/OEF veterans were recruited for the current study (mTBI: $n = 30$; normal controls [NC]: $n = 15$). All mTBI participants were diagnosed with a mild closed head injury during outpatient evaluation of

TBI at the Veterans Affairs San Diego Healthcare System. We used the following criteria delineated by the Department of Defense and Department of Veterans Affairs Traumatic Brain Injury Task Force[41] for mTBI: (1) AOC or LOC $\leq$ 30 minutes; (2) an initial Glasgow Coma Scale[42] score between 13 and 15 (which is often not available in a combat setting); (3) a period of posttraumatic amnesia of 24 hours or less; and (4) no visible lesions on magnetic resonance imaging (MRI) or computed tomographic scan. Loss of consciousness was not required for a TBI diagnosis, as any AOC lasting less than 24 hours following a head injury event, regardless of mechanism, was sufficient to warrant a diagnosis as defined by the United States Department of Defense.[43] As is typical of many military and civilian TBI studies, LOC or AOC duration was often determined via self-report given the paucity of patient medical information that is typically available surrounding mTBI events, particularly in combat settings.

A clinical neuropsychologist and radiologic technologist with more than 30 years of expertise (M.J.M.) in neuroimaging processing and analysis reviewed each scan to ensure no obvious lesions on structural images. In addition, an on-call clinical neuroradiologist reads any scans where there is a questionable abnormality determined by M.J.M. on participant's structural scans. No participants included in the current study demonstrated obvious lesions on standard neuroimaging. Exclusion criteria for all mTBI and NC participants included the following: (1) moderate to severe TBI (LOC > 30 minutes, posttraumatic amnesia > 24 hours, Glasgow Coma Scale score <12); (2) a history of other neurological condition (eg, multiple sclerosis, seizure disorder); (3) developmental learning disability; (4) current substance or alcohol abuse according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)- criteria; (5) preinjury metabolic or other diseases known to affect cognition (eg, diabetes); (6) history of psychiatric disorder prior to the TBI event; (7) current or pending litigation; (8) any contraindications to MRI scanning (eg, claustrophobia, shrapnel); or (9) below threshold cutoff scores on effort testing. Participants were, on average, approximately 2 to 4 years removed from their TBI event or events at the time of testing. Two additional participants were recruited but were later identified as outliers with respect to time since injury due to their TBI events occurring 8 and 12 years prior to testing. To equate group on this variable (time since injury), these outliers were excluded from all analyses; however, removal of those 2 participants did not change the results described later. All participants provided written informed consent, and all procedures complied with the local University of California San Diego (UCSD) and Veterans Affairs institutional review boards.

Neuropsychological Assessment

Participants were administered a battery of neuropsychological tests selected for its sensitivity to TBI in addition to the Beck Depression Inventory-II[44] (BDI-II) and the posttraumatic stress disorder (PTSD) checklist–military version (PCL-M).[45] The following tasks were used to evaluate EFs: the Wisconsin Card Sorting-Task 64-Card Version[46,47] and the Delis-Kaplan Executive Functioning System[48] Trail Making and Verbal Fluency Switching tests. Participants were also administered the Wide Range Achievement Test, Fourth Edition[49] (WRAT-4) Reading subtest as a measure of premorbid intellectual functioning. Demographically adjusted *T* scores[47] and scaled scores[48] were used for all analyses. Administration time for the entire neuropsychological battery was approximately 2.5 hours.

Reduced EF subgroup criteria

Participants were classified as having reduced EF performances if any of the following criteria were met: *T* score less than 40 for WCST Perseverative Responses (PR) or a Scaled Score less than 7 for D-KEFS Verbal Fluency Category Switching Total Correct or Trails Letter-Number Switching. Of the 13 mTBI participants identified with reduced EF performances, 6 demonstrated impairment on the WCST-PR, 5 on Category Fluency Switching and 7 on Letter-Number Switching. Nine of the 13 had impaired scores on only one of the three EF measures; 3 had impaired scores on two of the measures; and 1 was impaired on all three measures.

Symptom validity test measures

The Test of Memory Malingering[50] and the Forced-Choice Recognition Trial of the California Verbal Learning Test-II[51] were used to assess effort. Cutoff scores for identifying inadequate effort (Test of Memory Malingering Trial 2 < 45 and California Verbal Learning Test-II Forced-Choice Recognition Trial < 15) were based on recommendations from Tombaugh[50] and Moore and Donders,[52] respectively.

Brain Imaging

All participants underwent structural MRI and DTI on 3T General Electric MRI scanners housed within the UCSD Functional Magnetic Resonance Imaging (FMRI) Center on the UCSD La Jolla campus. Thirty-five participants (78%) were scanned with the scanner running the Excite HDx platform and, following the FMRI Center's scanner upgrade, data on 10 subjects were acquired with the scanner running the MR750 platform. Several studies support the reproducibility and robustness of FA across platforms.[53,54] Importantly, the gradients system

and application were not changed during the upgrade, and the postprocessing and analysis software techniques were consistent across the data. Specifically, we used the same b value (1500 s/mm^2) and number of diffusion gradients (61) and vector definitions, and all diffusion parameters (described later) were consistent before and after the scanner upgrade.

Structural scanning

A sagittally acquired high-resolution 3D T1-weighted anatomical MRI was collected with the following parameters: FOV 24 cm, 256 × 256 × 192 matrix, 0.94 × 0.94 × 1 mm voxels, 176 slices, TR = 20 ms, TE = 4.8 ms; flip angle 12°, scan time was roughly 7 minutes.

Diffusion tensor imaging

Diffusion tensor imaging images were collected with a dual spin echo EPI acquisition[55] with the following parameters: FOV = 240 mm, slice thickness = 3 mm, matrix size 128 × 128, in-plane resolution = 1.875 × 1.875, TR = 10 900 ms, TE = 93 ms. The 10 scans from the MR750 platform used identical scanning parameters though TR was shortened to 8000 ms to reduce scan time without affecting image quality. Specifically, given that the previous TR was much longer than necessary for accommodating the number of slices needed, the excess time in TR was reduced while holding all other parameters constant. This change is not expected to affect image SNR and contrast since, even at 8 seconds, the TR is still many times greater (> five times) than the T1 value of the brain tissue. Indeed, a simulation of the DTI signal equation in Matlab conducted by our lead neurophysicist (K.L.) showed that, assuming T1 of white matter at 3T is 840 ms (see Gelman et al[56]), the SNR difference in white matter between TR 8000 ms and TR 10 900 ms is only 0.007%. Across scanners, 24 slices were acquired with 61 diffusion directions distributed on the surface of a sphere according to the electrostatic repulsion model[57] and a b value of 1500 s/mm^2, as well as 1 T2 image with no diffusion weighting ($\beta = 0$). Two field maps with the same spatial parameters as those of the DTI scan were collected to correct for distortions due to magnetic field inhomogeneities. Total DTI acquisition time with field mapping was roughly 12 to 16 minutes.

Diffusion tensor imaging data processing

The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library[58] (FSL) was used for image processing. The 2 field maps were used to unwarp the EPI acquisitions. Images were then corrected for motion and eddy currents using the *eddy correct* FSL command. Each image was visually inspected for quality, and data from 3 participants did not meet quality standards and therefore were removed from analyses. The FSL program *bet* removed nonbrain voxels from the analysis. The FSL program *dtifit* fit a diffusion tensor model at each voxel to provide DTI variables such as FA and eigenvalues on a voxel-by-voxel basis. Per Song et al,[36] AD was defined by the principal eigenvalue (ie, AD = L1), and RD was defined as the average of the second and third eigenvalues: RD = (L2 + L3)/2.

Semiautomated regions of interest

Region of interest (ROI) placement was guided by a multistep process, and all ROIs were placed in MNI standard space as shown in Figure 1. First, the tract-based spatial statistics algorithm was used to align all FA images to a standard space, as well as to identify those fiber tracts common to all participants (see Smith et al[59] for a complete description). An FA threshold of 0.20 was used to restrict the white matter skeleton to voxels comprising only white matter and to reduce partial voluming effects. Next, ROIs were placed in the genu, body, and splenium subsections of the corpus callosum (CC), and bilaterally in the cingulum bundles and the anterior and posterior internal capsules (anterior internal capsule [AIC], posterior internal capsule [PIC]) following the International Consortium for Brain Mapping (ICBM-DTI-81) white matter labels' atlas available within FSL.[60] The cingulum bundle was segmented into posterior and anterior components wherein *anterior cingulum* was defined as those voxels anterior to the CC body and CC genu division, and *posterior cingulum* was defined as those voxels posterior to the CC body and CC splenium division. Two additional ROIs were placed in the prefrontal white matter identified as the dorsal prefrontal white matter and ventral prefrontal white matter. Prefrontal white matter was defined as all skeleton voxels anterior to the genu of the CC. The ventral/dorsal boundary was defined by a parasagittal line connecting the anterior and posterior commissures.[61] Mean FA, RD, and AD values for each ROI were extracted for each subject and exported to SPSS Statistics 18, 2009 (SPSS Inc, Chicago, Illinois) for statistical analyses.

Statistical Analyses

Group comparisons were conducted using analysis of variance followed by contrast testing (*t* tests), including comparisons of the EF subgroup status and AOC versus LOC group comparisons of the DTI metrics. Effect size statistics (Cohen *d*) for the significant *P* for each of the group comparisons were also calculated. Categorical data were analyzed using likelihood-ratio chi-square tests (eg, LOC by EF subgroups) because of the relatively small sample size. Multiple comparison corrections were conducted using false discovery rate methodology[62] for the primary DTI analysis between reduced and

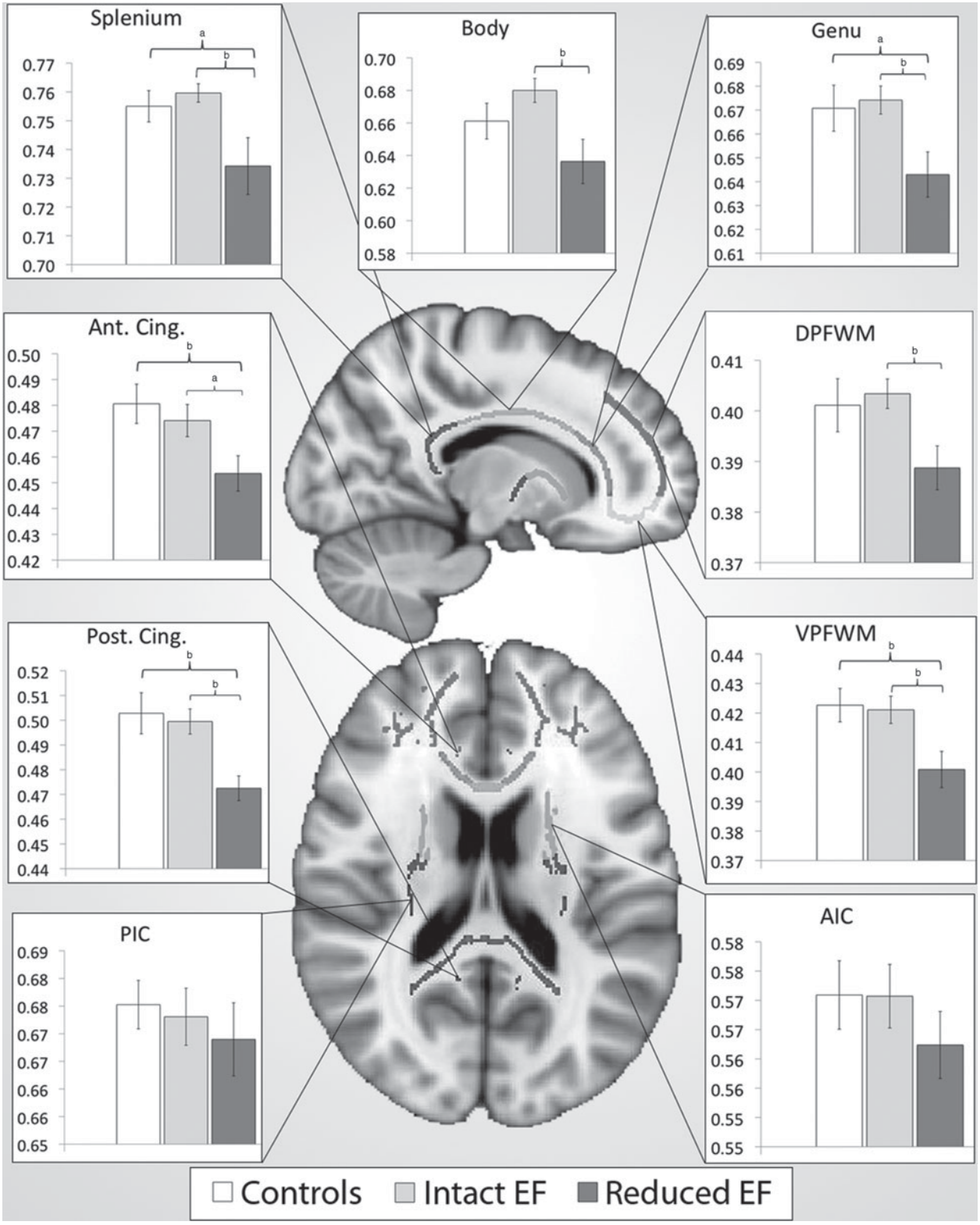

Figure 1. Atlas-based ROI placement and group comparisons of FA values. Placement of the TBSS-derived white matter skeleton regions of interest in standard space on a T1 image. AIC indicates anterior internal capsule; Ant Cing, anterior cingulum bundle; DPFWM, dorsal prefrontal white matter; EF, executive functions; FA, fractional anisotropy; HC, healthy controls; PIC, posterior internal capsule; Post Cing, posterior cingulum bundle; ROI, region of interest; TBSS, tract-based spatial statistics; VPFWM, ventral prefrontal white matter. Error bars represent SEM. [a]*P* corrected < .10, [b]*P* corrected < .05.

intact EF subgroups and control participants with false discovery rate set at 0.05. Multiple comparison corrections were not performed on the LOC versus AOC analyses because of their exploratory nature.

RESULTS

TBI and NC Group Demographic and Clinical Characteristics

Participants' demographic and injury characteristics are presented in Table 1. Although the TBI group demonstrated 1 year less education on average, their estimated premorbid intellectual functioning as measured by the WRAT-4 did not differ between groups, and the groups did not significantly differ on age or sex distribution. As expected, however, the mTBI group evidenced significantly higher levels of depressive (BDI-II, $P < .01$) and PTSD-related symptomatology (PCL-M, $P < .001$). However, the 2 mTBI subgroups did not differ from one another on either measure of depressive or PTSD-related symptoms, nor did they differ on any of the TBI injury severity characteristics with the exception of LOC percentage ($P = .02$; see Table 1).

Mild TBI Versus NC Group Comparisons

As shown in Table 2, comparisons of the regional DTI values between the mTBI and NC groups did not reach significance ($P > .10$). In terms of neuropsychological performance, the mTBI group performed significantly worse than the NC participants on category fluency switching (Cohen $d = 0.80$, $P = .002$) (see Table 3). Importantly, a post hoc analysis of covariance adjusting for BDI-II and PCL-M scores found that the lower score on category fluency switching remained significant, suggesting that comorbid psychiatric disturbance did not account for the lower scores observed in the mTBI sample.

Reduced Versus Intact EF mTBI Subgroup Comparisons

Approximately 43% (13/30) of the mTBI sample demonstrated reductions on EF measures based on the criteria described previously. As shown in Table 1, there were no significant differences on demographic characteristics or psychiatric symptomatology between the 2 subgroups. Of the injury characteristics, LOC status significantly differed between subgroups, with higher rates of LOC in the reduced EF subgroup ($P = .02$). The number of months since the most recent mTBI did not significantly differ between subgroups ($P = .06$), nor was there a statistically significant difference in the proportion of participants whose most recent mTBI was within the past 2 years. In addition, mTBI subgroups did not differ in frequency of blast exposure or total number of mTBI events (all $P > .40$).

Executive Function mTBI Subgroup Differences by DTI Indices of White Matter Integrity

Table 2 lists the means, standard deviations, and results of comparisons of the control group and 2 mTBI subgroups on the DTI measures across each of the regions of interest. The group FA comparisons for each ROI are further illustrated in Figure 1. It is important to note that the *intact* EF mTBI subgroup did not significantly differ from *control* participants on any DTI measure (including all FA and radial and AD measures) across all ROIs (all $P > .10$). However, as can be seen in Figure 1, statistically significant (P corrected $< .05$) FA reductions with large effect sizes were found for the reduced EF mTBI subgroup when compared with the intact EF subgroup in the dorsal prefrontal white matter (Cohen $d = 1.07$), ventral prefrontal white matter (VPFWM) (Cohen $d = .99$), CC genu (Cohen $d = 1.08$), CC body (Cohen $d = 1.11$), CC splenium (Cohen $d = 1.00$), the posterior cingulum (Cohen $d = 1.37$), and with a trend toward significance (P corrected $< .10$) in the anterior cingulum (Cohen $d = .81$). These findings were unchanged after adjusting for months since injury in analyses of covariance. All other FA ROIs (ie, AIC and PIC) did not reach significance (all $P > .10$). When compared with control participants, the reduced EF mTBI subgroup showed significantly lowered (P corrected $< .05$) FA values in the VPFWM (Cohen $d = .98$), the anterior cingulum (Cohen $d = .97$), and the posterior cingulum (Cohen $d = 1.28$) with trends in this direction for the CC genu (Cohen $d = .79$) and CC splenium (Cohen $d = .73$).

The reduced EF mTBI subgroup showed significantly higher (P corrected $< .05$) RD than the intact EF subgroup within the posterior cingulum (Cohen $d = 1.21$), with trends (P corrected $< .10$) in the VPFWM (Cohen $d = 1.00$), the CC body (Cohen $d = .92$), and the CC genu (Cohen $d = .77$). Compared to NCs, there was a trend (P corrected $< .10$) toward higher RD in both the VPFWM (Cohen $d = .98$) and posterior cingulum (Cohen $d = .88$) in the reduced mTBI subgroup. Regarding AD, the reduced EF mTBI subgroup showed significantly lower (P corrected $< .05$) AD values within the AIC (Cohen $d = 1.19$) and the PIC (Cohen $d = 1.21$) relative to the intact EF subgroup. All other AD ROIs did not reach significance, and there were no significant differences between the control and reduced EF mTBI groups.

Exploratory Group Comparisons by LOC Versus AOC

Because the reduced EF subgroup demonstrated a higher percentage of participants with LOC compared with the intact EF subgroup (see Table 1), exploratory

TABLE 1 *Demographic, TBI severity, and psychiatric characteristics of control participants and mTBI subgroups (unimpaired and impaired executive function [EF])*

	Control	TBI	*P*	Intact EF	Reduced EF	*P*
n	15	30	. . .	17	13	. . .
Age, y	32.9 (8.2)	30.7 (9.3)	.42	28.9 (8.0)	32.8 (10.8)	.27
Years of education	14.3 (1.8)	13.3 (1.3)	.04	13.4 (1.5)	13.3 (0.9)	.93
WRAT-4 reading (SS)	105.7 (9.0)	104.2 (10.8)	.63	104.3 (9.2)	104.0 (13.1)	.94
% Male	73%	87%	.27	88%	85%	.77
% Caucasian	73%	57%	.28	65%	46%	.31
BDI-II	5.1 (10.1)	17.5 (11.6)	.001	16.4 (8.7)	17.5 (5.4)	.56
PCL-M	22.8 (14.5)	42.0 (15.6)	<.001	43.1 (14.2)	41.0 (18.6)	.66
Mean number of mTBIs	. . .	. . .	. . .	2.9 (2.5)	3.1 (2.4)	.90
Months since mTBI	. . .	. . .	. . .	43.5 (21.8)	28.2 (19.1)	.06
% mTBI within past 2 y	. . .	. . .	. . .	24%	46%	.19
% >1 mTBI	. . .	. . .	. . .	76%	69%	.66
% Combat mTBI	. . .	. . .	. . .	65%	69%	.79
% Reporting any LOC at TBI	. . .	. . .	. . .	41%	85%	.02
% Reporting blast related mTBI	. . .	. . .	. . .	82%	69%	.40

Abbreviations: BDI-II, Beck Depression Inventory-2; LOC, loss of consciousness; mTBI, mild traumatic brain injury; PCL-M, Posttraumatic Stress Disorder Check List—Military Version; SS, scaled score; WRAT-4, Wide Range Achievement Test, Fourth Edition.

analyses were conducted to investigate the associations among LOC, cognition, and white matter integrity. The mTBI sample as separated by LOC/AOC status (LOC [$n = 18$] vs AOC [$n = 12$]) did not significantly differ in terms of age, education, WRAT-Reading scores, or injury and psychiatric characteristics ($P > .05$). Group comparisons of AOC versus LOC on the individual EF scaled scores, and *T* scores were not significantly different ($P > .05$). However, compared with NCs, the LOC subgroup was found to have significantly lower scaled scores on both the D-KEFS Category Fluency Switching Total Correct ($M_{Control} = 12.5$, $SD_{Control} = 3.2$, $M_{LOC} = 9.2$, $SD_{LOC} = 2.6$, $P = .01$, Cohen $d = 0.99$) and D-KEFS Trails Letter-Number Switching ($M_{Control} = 9.9$, $SD_{Control} = 2.2$, $M_{LOC} = 7.7$, $SD_{LOC} = 3.8$, $P = .046$, Cohen $d = 0.74$).

An analysis of the regional DTI values did reveal significant group differences in white matter integrity. As can be seen in Figure 2, the LOC subgroup evidenced significantly higher RD in the VPFWM than the AOC subgroup RD $\times 10^{-3}$ mm^2/s ($M_{AOC} = 0.54$, $SD_{AOC} = 0.02$, $M_{LOC} = 0.57$, $SD_{LOC} = 0.04$, $P = .02$, Cohen $d = .89$) with a trend toward lower VPFWM FA ($M_{AOC} = 0.42$, $SD_{AOC} = 0.02$, $M_{LOC} = 0.41$, $SD_{LOC} = 0.02$, $P = .07$, Cohen $d = .71$). When compared with control participants, VPFWM RD was significantly higher in the LOC subgroup ($M_{Control} = 0.54$, $SD_{Control} = 0.03$, $M_{LOC} = 0.57$, $SD_{LOC} = 0.04$, $P = .03$, Cohen $d = .84$) and VPFWM FA was significantly lower in the LOC subgroup ($M_{Control} = 0.42$, $SD_{Control} = 0.02$, $M_{LOC} = 0.41$, $SD_{LOC} = 0.02$, $P = .04$, Cohen $d = .85$).

DISCUSSION

Our finding that reduced EF performance may be present in a subgroup of OEF/OIF veterans with a history of mTBI is consistent with other reports showing chronic neuropsychological difficulties following mTBI.[5–7] Results further revealed that this subgroup of mTBI participants demonstrated significantly lower white matter integrity (FA) when compared with either mTBI participants with intact EF or healthy control participants within prefrontal, commissural, and posterior association tracts, and findings are consistent with other reports showing lower white matter integrity in a mTBI subgroup with protracted recovery.[21,30] In addition, the RD analysis suggests that compromised myelin integrity may contribute to the lower white matter integrity within frontal white matter, the CC, and posterior cingulum within this reduced EF subgroup. These findings were in contrast to the mTBI group as a whole, which did not significantly differ from our NC group in terms of white matter integrity. Taken together, our results (1) demonstrate that executive dysfunction is strongly associated with white matter integrity in a subgroup of OEF/OIF veterans with mTBI across frontal and more posterior regions and (2) further suggest that the observed impairment in executive functioning, in some cases, may be a result of persisting neuronal damage from mild TBI.

The exploratory LOC analyses offer some provisional support to the notion that the observed EF reductions and concomitant white matter compromise in our sample of mTBI participants are perhaps related

TABLE 2 *Means (M), standard deviations (SD), and group comparisons of regional values on diffusion tensor imaging in control participants and mTBI subgroups (intact and reduced executive function [EF])*

		Control		Intact EF		Reduced EF		*P*		
	ROI	M	SD	M	SD	M	SD	Control vs TBI	Intact vs Reduced EF	Control vs Reduced EF
FA	DPFWM	0.40	0.02	0.40	0.01	0.39	0.02	.46	.007[a]	.05
	VPFWM	0.42	0.02	0.42	0.02	0.40	0.02	.15	.01[a]	.009[a]
	CC genu	0.67	0.04	0.67	0.02	0.64	0.03	.35	.007[a]	.03[b]
	CC body	0.66	0.04	0.68	0.03	0.64	0.05	.99	.006[a]	.12
	CC splenium	0.76	0.02	0.76	0.01	0.73	0.04	.61	.01[a]	.03[b]
	Ant Cing	0.48	0.03	0.47	0.03	0.45	0.03	.09	.04[b]	.01[a]
	Post Cing	0.50	0.03	0.50	0.02	0.47	0.02	.08	.001[a]	.003[a]
	Ant IC	0.57	0.02	0.57	0.02	0.56	0.02	.59	.31	.31
	Post IC	0.68	0.02	0.67	0.02	0.67	0.02	.55	.62	.42
RD $\times 10^{-3}$ mm^2/s	DPFWM	0.55	0.03	0.55	0.02	0.56	0.03	.33	.23	.14
	VPFWM	0.54	0.03	0.54	0.03	0.57	0.04	.21	.012[b]	.009[b]
	CC genu	0.39	0.04	0.37	0.03	0.42	0.05	.34	.04[b]	.05
	CC body	0.40	0.05	0.38	0.04	0.43	0.07	.83	.02[b]	.11
	CC splenium	0.29	0.02	0.29	0.01	0.31	0.04	.53	.06	.09
	Ant. Cing.	0.51	0.04	0.52	0.03	0.54	0.04	.18	.11	.04
	Post. Cing.	0.45	0.02	0.44	0.01	0.47	0.02	.35	.003[a]	.02[b]
	Ant. IC	0.40	0.02	0.41	0.02	0.40	0.03	.56	.67	.79
	Post. IC	0.33	0.02	0.33	0.02	0.32	0.02	.75	.29	.71
AD $\times 10^{-3}$ mm^2/s	DPFWM	1.02	0.03	1.04	0.03	1.03	0.03	.39	.39	.83
	VPFWM	1.07	0.04	1.07	0.04	1.09	0.03	.71	.33	.40
	CC genu	1.39	0.07	1.40	0.05	1.39	0.06	.64	.37	.94
	CC body	1.40	0.05	1.42	0.04	1.40	0.06	.33	.29	.81
	CC splenium	1.40	0.05	1.42	0.06	1.37	0.05	.95	.04	.20
	Ant Cing	1.14	0.07	1.15	0.04	1.13	0.05	.85	.48	.65
	Post Cing	1.04	0.05	1.03	0.03	1.01	0.05	.30	.23	.14
	Ant IC	1.09	0.05	1.12	0.04	1.08	0.04	.71	.003[a]	.24
	Post IC	1.17	0.05	1.19	0.04	1.13	0.05	.81	.003[a]	.05

Abbreviations: AD, axial diffusivity; Ant, anterior; CC, corpus callosum; Cing, cingulum; DPFWM, dorsal prefrontal white matter; FA, fractional anisotropy; FDR, false discovery rate; IC, internal capsule; mTBI, mild traumatic brain injury; Post, posterior; RD, radial diffusivity; ROI, region of interest; VPFWM, ventral prefrontal white matter.

[a]FDR *P* corrected < .05

[b]FDR *P* corrected < .10

TABLE 3 *Means (M) and standard deviations (SD) of neuropsychological tests of executive function (EF) for the control and mild traumatic brain injury (mTBI) groups, and for the mTBI subgroups split by executive function performance*

	Control		mTBI		Intact EF		Reduced EF		*P*		
Measure	M	SD	M	SD	M	SD	M	SD	Control vs mTBI	Intact vs Reduced EF	Control vs Reduced EF
WCST Perseverative Responses T-Score	47.1	5.8	48.6	8.7	52.2	7.7	44.2	8.1	.56	.01	.34
D-KEFS Category Switching SS	12.5	3.2	9.4	3.0	10.2	2.5	8.4	3.5	.003	.12	.002
D-KEFS Trails Switching SS	9.9	2.2	8.5	3.5	10.4	1.9	6.1	3.6	.15	<.001	.001

Abbreviations: D-KEFS, Delis-Kaplan executive function system; SS, scaled score; WCST, Wisconsin Card Sorting Test.

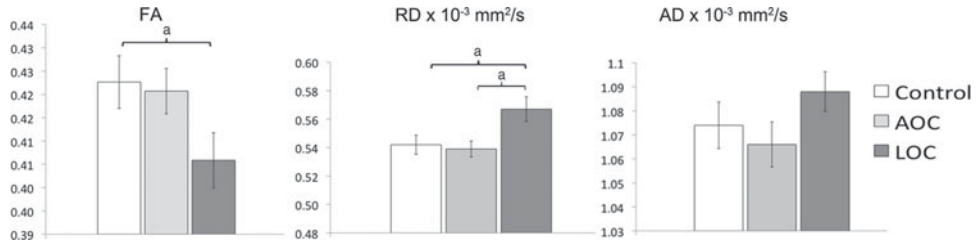

Figure 2. Ventral prefrontal white matter diffusion tensor imaging indices by LOC/AOC status in mild traumatic brain injury compared to control participants. AD indicates axial diffusivity; AOC, alteration of consciousness; FA, fractional anisotropy; LOC, loss of consciousness; RD, radial diffusivity. Error bars represent SEM. [a]$P < .05$.

to neurotrauma history and are not solely because of normal variation in EF scores. First, LOC was associated with higher rates of impaired EF scores when compared with those reporting AOC (without LOC). This distinction is generally consistent with some mTBI studies that have tied LOC to poorer health outcomes and a more prolonged recovery.[1,39,40] However, the effect of LOC in these studies was significantly attenuated after accounting for psychiatric symptomatology such as PTSD symptom severity. Moreover, Belanger et al[38] reported that PTSD symptom severity, but not LOC, was associated with increased reporting of postconcussive symptoms. In contrast, in our sample, LOC was not associated with higher levels of psychiatric distress when compared with those who did not lose consciousness.

In addition, the DTI findings show that LOC was associated with ventral prefrontal white matter integrity degradation, as indicated by RD and AD. The specificity of these findings suggests potential differences in frontal myelin and neural integrity in terms of injury severity (indexed by LOC vs AOC). The injury severity findings are further consistent with other recent studies indicating persisting white matter damage associated with mTBI in OEF/OIF samples,[63,64] though they contrast with the results reported by Levin et al[65] wherein no main effect or graded severity effect (mild vs moderate) of TBI was found. This difference in study findings may be related to differences in sensitivity of the DTI sequence employed (eg, our data were acquired using a 61- vs 32-direction sequence); however, it is important to note that Levin et al[65] examined only blast-related mild to moderate TBI, whereas most of our mTBI sample (56%) reported a mixed history of both blunt and blast force mTBI and multiple mTBI events. Recently, Goldstein et al[66] found neuropathologic evidence for persistent chronic traumatic encephalopathy in the brains of military veterans with blast exposure and/or blunt concussive injury, suggesting that TBI induced by different insults under different conditions can trigger common pathogenic mechanisms leading to similar neuropathology and sequelae. Notably, within the small autopsy sample they examined, the effects of blast exposure, blunt concussive injury, and mixed trauma were indistinguishable. Note too that Belanger et al[67] failed to show neuropsychological differences between blast versus blunt trauma TBI subgroups. Given the high prevalence of blast and/or blunt concussive exposures among OEF/OIF veterans, the chronic effects of TBI and potential for long-term chronic traumatic encephalopathy–linked neuropathologic changes among our retired veterans warrants further investigation.

The elevated psychiatric symptom ratings (ie, PTSD-related or depressive symptom ratings) in the mTBI group relative to control participants are consistent with other reports that self-reported neurotrauma, in general, and psychiatric distress are highly comorbid among OEF/OIF veterans.[1,65,68] However, our EF subgroups did not significantly differ in PTSD-related or depressive symptom ratings, suggesting that psychiatric distress alone cannot account for the observed group differences in white matter integrity. In addition, the *intact* EF mTBI subgroup did not differ from NC participants on any of the DTI or cognitive comparisons, despite their higher levels of PTSD-related and depressive symptom ratings, further supporting the notion that psychiatric distress did not contribute to the regional white matter differences.

Our finding of worse performance on a speeded test of category fluency switching in the mTBI group relative to control participants, even after statistically adjusting for the higher rates of depression and PTSD symptom severity scores, somewhat contrasts with the results of meta-analytic studies that generally show no or very mild effects of mTBI.[8–12] However, the clinical significance of this finding is limited as the mean performance of the mTBI group, as a whole, falls within the average range. Category fluency is thought to rely on both frontal and temporal regions, and the added switching component may draw more heavily on frontally mediated attentional and EF processes.[69] Indeed, Zakzanis et al[70] report that switching within category fluency tasks may be especially sensitive to frontal brain dysfunction. It is possible then that the observed damage to frontal and posterior association tracts in the reduced EF subgroup relative to control participants may collectively

disrupt the concerted integration of the many cognitive subprocesses responsible for optimal performance on this task.

Our findings are derived from one of the few investigations of cognitive dysfunction as it relates to white matter integrity in a sample of OEF/OIF veterans. None of the participants in the current sample were involved in litigation, and none of the 45 participants on whom the analyses were performed evidenced performances below expectations on symptom validity testing. Our exclusion criterion based on symptom validity testing may, in part, explain some of the differences between the results of our study and those of other studies where it was not conducted or reported (eg, Levin et al,[65] Hoge et al [1]). It is noteworthy that the study by Levin et al,[65] which did not show DTI differences between OEF/OIF veterans with blast TBI and controls, did not report effort testing in their sample. If some participants with insufficient effort were included in their sample, one might expect to see cognitive test score differences but no DTI differences, and inconsistent or nonsignificant correlations of DTI variables with symptom measures, all of which were demonstrated in their study. Our finding of comparable PTSD- and depressive-symptom severities across subgroups, combined with formal effort testing, further supports the notion that psychiatric distress or insufficient effort were not contributors to the cognitive test score findings or regional white matter differences in our reduced mTBI subgroup.

There are limitations to this study that warrant discussion. First, our data are cross-sectional and injury characteristics (e.g., LOC and AOC) were largely gleaned from self-report, and thus it is possible that the observed differences in FA and neuropsychological performance may reflect premorbid differences that are perhaps unrelated to the mTBI. However, the groups were comparable on educational attainment and reading level. Second, the generalizability of our findings to single-event mTBIs is limited as most of our mTBI participants endorsed having sustained more than 1 TBI. Third, a little more than 40% of our clinical sample showed reductions on tests of EF, although the impairment criteria described earlier were designed to be liberal to increase our sensitivity to detect possible impairment for the research purposes specific to this study. They are not meant to represent the basis for a clinical diagnosis of a cognitive disorder. Fourth, insufficient sample size limited our ability to study the effects of blast-only ($n = 5$) versus blunt-only ($n = 9$) injury mechanisms, though as noted the *presence* of any blast injury was not associated with EF impairment or LOC. Moreover, at present, those investigations comparing blast-only and blunt-only mTBI in OEF/OIF veterans have found no strong evidence of disparate outcomes whether in postconcussive symptom reporting or neuropsychological performance.[38,67] Finally, the tensor model of diffusion-weighted imaging is limited in regions with more complex architecture (eg, where crossing fibers exist within a single voxel), and thus the measured FA may be attenuated in some regions.[34] Although this possibility may have altered the FA measures to some degree, this effect is assumed to be consistent across the groups such that differences in diffusivity measures, while imprecise, continue to signify altered white matter integrity.

CONCLUSIONS

Although there were no direct main effects of mTBI demonstrated in the context of this study, we identified a subgroup of OEF/OIF veterans with mild, but demonstrable, EF reductions and concomitant brain changes associated with their history of mTBI, suggesting that neuronal and cognitive recovery may be protracted in some cases, especially in patients who experienced an LOC. Given the lack of differences between those with and without EF decrements on PTSD-related or depressive symptom severities, it is less likely that psychiatric symptomatology can fully explain the pattern of cognitive and brain findings. Clearly, additional research within this population is warranted to better understand the cognitive and neurostructural effects of mild TBI and to better identify veterans who may continue to struggle cognitively (and potentially psychiatrically) in the aftermath of their brain injuries.

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